REMARKS

1. **Information Disclosure Statement**

The Examiner indicates that the Information Disclosure Statement filed on July 23, 2004 does not comply with the rules because it did not include a legible copy of each of the non-U.S. Patent literature references. But the submission on July 23, 2004 was simply of a copy of the IDS previously filed on October 19, 2000 because the Examiner had indicated that the IDS was missing from the file (see paragraph 6 on page 4 of the previous Office Action dated March 23, 2004). In either event, a new IDS with a copy of each of the literature references will be submitted.

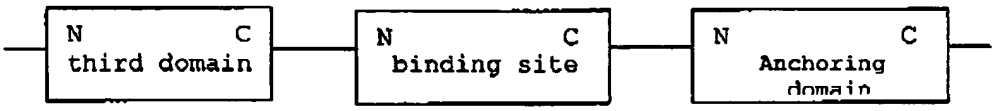
2. **Rejections Under 35 U.S.C. § 112**

Claims 1-24 and 27-33 have been rejected under 35 U.S.C. § 112, second paragraph. These rejections are respectfully traversed.

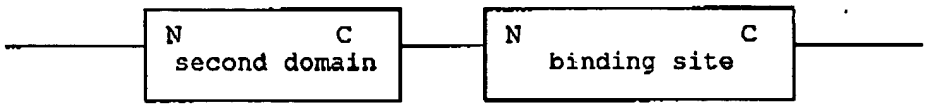
2.1. The Examiner has requested clarification of the terms "further domain" and "additional domain". The claims have been amended to better clarify the relationship of the various "domains". But the following explanation is provided to further aid the Examiner in understanding the claimed invention.

First of all, the present invention is not solely related to a biological display system, but rather to a method for the identification of a binding site domain which is characterized in that the binding specificity is not lost when that binding site is cloned in a position C-terminal of a different domain. As described in the present application, the invention involves the following overall method:

Step 1: Identification of a specific binding site domain as part of a fusion protein which comprises a "third domain" and an "anchoring" domain:



Step 1 is followed by step 2 wherein the third domain is replaced by a second domain. The specific binding capacity of the binding site domain is not lost:



It is important to note that the invention is characterized by the positioning of the binding site domain with respect to the third domain or, respectively, with respect to the second domain. The C-terminal positioning of the binding site domain retains binding capacity of the binding site. The positioning of the anchoring site is also reflected in Figure 5.3 of the specification as filed and is also defined because it is the N-terminus of the C-terminal CT domain of the gene III product from filamentous phages which enables anchoring of the phage. However, the positioning of the anchoring amino acids might also be different, depending on what display system is used. As explained, it is the positioning of the third domain or, respectively, the second domain vis-à-vis the binding site domain that characterizes the present invention. It is also of note that the "third domain" is different from the "second domain", as explained below.

The present invention relates to the identification of single binding sites that can subsequently be joined as multi-compatible modules with many different further domains, (i.e. a second domain) to form final bi- or multifunctional constructs. The present invention does not relate to the display and selection of pre-defined bi- or multifunctional constructs. Accordingly and most importantly, said second domains themselves are not subjected to the selection process of these binding sites. Since many of such second domains cannot be approximately expressed in certain display systems (this is, e.g. true for B7-1 due to its glycosylation in *E.coli* based phage display systems) it is essential that binding sites can be selected from libraries without the requirement of such second domain being itself present during the display and selection process. In accordance with the present invention, it was surprisingly found that the

binding site that is C-terminally fused with such N-terminal second domains is suitable for such a selection process. Selection for the general property of antigen binding in a C-terminal position, irrespective of which domain occupies the N-terminal position in a final bi- or multifunctional construct, could be achieved by employing an additional domain (i.e. the third domain) at the N-terminus of the binding site to act as a surrogate for possible different N-terminal second domains during the process of display and selection (it is important to note that the additional (third) domain is not identical with the further (second) domain). This additional (third) domain can be adapted to the exigencies of the display system used as has been done in the present invention with the N2-domain of the gene III product of filamentous phage in an *E.coli* based phage display system.

To summarize, the teachings of the present application do not merely aim at the observation that C-terminally located binding sites selected for binding to an epitope in the presence of a third domain located at the N-terminus (e.g. N2) do indeed bind their epitope in the presence of this additional domain. Rather, the work underlying the present application has resulted in the surprising observation that binding sites identified by this method retain the binding activity for their epitope when said N-terminal third domain is replaced by an unrelated N-terminal second domain (e.g. B7-1) which was not present itself during the display and selection process. Thus, the method of the invention has indeed been shown to select for binding sites that exhibit the general property of binding to their epitope in a C-terminal position irrespective of which further domain occupies the N-terminal position in a final bi- or multifunctional construct. The general applicability of the method of the invention could successfully be demonstrated for a variety of further domains: Apart from B7-1, a chemokine and an scFv-fragment served as further domains while the binding activity of the binding site was retained.

2.2. With respect to the objection regarding the phrase "an amino acid sequence that mediate anchoring of the fusion protein", claim 1 has been amended in a manner which is believed to make clear the relationship of the anchoring amino acid to the other two domains in the fusion protein.

2.3. The Examiner has made some further objections with respect to terminology in claims 2, 13, 22, 24, 30 and 32. Those claims have also been amended in a manner believed to overcome the objections.

In view of the above, reconsideration and withdrawal of the rejections under § 112 are requested.

3. Rejections Over Prior Art

3.1 ***Rejection of claims 1-8, 10-16 and 19-21***

Claims 1-8, 10-16 and 19-21 have been rejected as being obvious over Mack et al. in view of Barbas et al. This rejection is respectfully traversed.

Applicants do not agree that it would be *prima facie* obvious to combine the two cited references, nor that combining the references would result in the present invention.

The bi-specific molecules of Mack et al. represent defined binding domains (page 7022, first column (i.) of reference). The reference does not at all disclose a "display library". Furthermore, the binding site domains are expressed in a eukaryotic expression system, and not in a prokaryotic expression system (see page 7022, column 1, (iii)).

Barbas et al. describes the prokaryotic expression of monovalent Fab fragments with a C-terminal amino acid sequence for anchoring of the Fab fragment on the surface of the display system. Mack et al., however, expressively teaches that in prokaryotic expression systems bivalent constructs cannot be functionally expressed, see page 7023, fifth paragraph.

It would therefore not have been obvious to combine the teaching of Mack et at. and Barbas et al. It would not have been obvious that the bivalent constructs of Mack et al. would be expressed together with a C-terminal domain of gene III for using a display system.

Furthermore, it is of note that the bi-specific fusion proteins of Mack et at. lack the amino acid sequence which is responsible for anchorage on a surface of the display system. No identification of specific binding site domains in a biologically display system is disclosed. The fusion proteins of Barbas et at. do not comprise any "additional domain"or "third domain". Furthermore, Mack et al. expressively teaches away from the possibility to functionally express bi-specific molecules in prokaryotes.

For these reasons, Applicant submit that no combination of Mack et al. and Barbas et al. can properly be considered to render the claimed invention *prima facie* obvious.

3.2. Rejection of Claim 9

Claim 9 has been rejected under 35 U.S.C. 103 as being obvious over Mack et al. in view of Barbas et al. and further in view of Borrebaeck et al. (US Patent 6,027,930). This rejection is respectfully traversed.

The distinctions of the present invention over Mack et al. and Barbas et al. are discussed above. With respect to Borrebaeck et al., this reference describes a method for identification of binding site domains in the Fab format. But is noted that the deleted gene III in the reference does not contain the N2-domain anymore, since the N2-sequence is part of the deleted region 1525-2646. This is completely contrary to the Examiner's

interpretation of the reference so that it is clear that use of the N2-domain in the present invention cannot be in any way be considered obvious in view of the cited references.

3.3. Rejection of Claims 17 and 18

Claim 17 and 18 have been rejected as being obvious over Mack et al. in view of Barbas et al. in further in view of Lindhofer et al. (US Patent 6,551,592). This rejection is respectfully traversed.

Again, the distinction of the present invention over Mack et al. and Barbas et al. are discussed above. The Examiner urges that Lindhofer et al. describes co-stimulatory molecules suitable for display library systems. But co-stimulatory molecules are specific forms of the "further domain" or "second domain" in the present invention. That second domain has been cloned N-terminal at the already optimized binding site domain. But such second domain, as discussed above, usually cannot be used for a "display library" system. As such, no combination of the references cited by the Examiner can properly be considered to render the present invention *prima facie* obvious.

In view of the above, reconsideration and withdrawal of the prior art rejections are requested.

4. Allowable Subject Matter and Scope of Allowed Claims

The Examiner has noted that claims 22-24 and 28-33 if re-written to overcome the rejections under § 112. As noted above, the claims have been amended in a manner believed to obviate the § 112 rejections, so that it is believed that those claims should now be in condition for allowance.

However, the Examiner further urges that non-elected SEQ ID NOs: 60-74 and 76-77 are considered patentably distinct from each other, and apparently patentably distinct from SEQ ID NO. 75. Thus, without explicitly saying so, the Examiner seems to suggest that any allowable claims in the present application must be limited to only SEQ ID NO. 75. Applicants submit that this would be an improper restriction of the claims, without any proper statutory or regulatory basis on the part of the Examiner.

In accordance with acceptable procedures, the Examiner issued an election of species requirement, and Applicant elected the species identified by SEQ ID NO. 75. With the indication that the species of SEQ ID NO. 75 is allowable, **it is now incumbent upon the Examiner to expand the search and examination of the claims to encompass more than just this one species**. As set forth in MPEP § 803.02, "once the elected species is found allowable over the prior art, the remaining scope of the claim will be examined fully with respect to the elected species in further to the extent necessary to determine patentability".

The Examiner seems to take the position that if the individual amino acid sequences are patentably distinct from each other, then the claims must be limited to a single elected amino acid sequence species, since the claims cannot encompass more than one patentably distinct invention. But this completely misconstrues the proper meaning of restriction requirements and election of species. The statutory basis for an Examiner to make a Restriction Requirement between groups of claims is 35 U.S.C. § 121. But that authority does not provide a basis for an Examiner to attempt to restrict from within a claim. As explained by the Federal Circuit's predecessor court (CCPA);

> "It is apparent that § 121 provides the Commissioner with the authority to promulgate rule designed to restrict an application to one of several claimed invention when those inventions are found to be "independent and distinct". It does not, however, provide a basis for an Examiner acting under the authority of the Commissioner to reject a particular claim on the same basis." *In re Weber*, 198 USPQ 334(Rich, J. concurring).

In the present application, Applicants are entitled to examination of their generic claims, such as claim 1, which are not limited to individual species or amino acid sequence. While the Examiner appropriately requested an election of species to begin examination, the Examiner may not simply refuse to examine additional species and thereby refuse to examine Applicants' proper broad generic claims. Such a refusal is tantamount to an attempt to reject the claim under 35 U.S.C. § 121, a rejection which has been viewed with disapproval by the court. Although the Examiner points to the potential inclusion of distinct

sequences or species, the number of potentially distinct species is irrelevant as stated by Judge Rich:

> "It is elementary patent law that the number of "species" "cover" by a patent having a generic claim is virtually without limit not withstanding the limitation of rule 141 to five species "specifically claimed". So that the discretionary power to limit one application to one invention is no excuse at all for refusing to examine a broad generic claim - no matter how broad, which means no matter how many independently patentable distinct inventions may fall within it." *Id*

Accordingly, while Applicants appreciate the indication allowable subject matter relative to SEQ ID NO. 75, Applicants are entitled to examination of their broader generic claims, so the Examiner is requested to proceed as required by the MPEP, to examine the remaining scope of the Applicants' claims.

In summary, Applicants have amended the claims to overcome the Examiner's rejections under 35 U.S.C. § 112, and have fully explained why the claims are patentably distinct over cited prior art. Moreover, Applicants have further explained why there is no proper basis for the Examiner to restrict the claims to only be elected species identified by SEQ ID NO. 75. Therefore, it is submitted that all of the claims are in condition for allowance, and early issuance of a Notice of Allowance is, therefore, requested.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), the Applicant respectfully petitions for a three (3) month extension of time for filing a response in connection with the present application and the required fee of $510.00 is to be charged to deposit account 02-2448.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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